AF/1639

CASE 4-30730A

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF
AUER ET AL.
APPLICATION NO: 09/754,958
FILED: JANUARY 5, 2001
FOR: FLUORESCENT DYES (AIDA) FOR SOLID PHASE AND SOLUTION PHASE SCREENING

Art Unit: 1639
Examiner: Maurie Garcia Baker

#16 Sub 98 10/9/03

MS: Appeal Brief
Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

APPEAL BRIEF

Sir:

This appeal is lodged in response to a Final Rejection dated May 6, 2003 finally rejecting claims 12-16. Applicants request reconsideration of the rejections and reversal of the Final Rejection.

1. Real Party In Interest:

The real party in interest is Novartis AG

2. Related Appeals and Interferences:

None.

3. Status of Claims:

Claims 12-16 are pending. Claims 12-16 (Appendix I) are under Final Rejection and are now on appeal. Claims 17-21 (Appendix II) are non-entered.

4. Status of the Amendments:

All the original claims have been canceled. Claims 12-16 were added by amendment dated September 9, 2002. An amendment under 37 CFR 1.116 dated June 10, 2003 replacing 12-16 by 17-21 was not entered.

5. Summary of the Invention:

The claims on appeal are directed to a) compounds comprising the partial structures defined by formulae II or III:

A-B-D-C-D′- (Formula (II))

A-B-D- and -D′-C (Formula (III))

and b) conjugates.

6. Issues:

1. Whether there is a written description of the claimed invention.

2.. Whether the claimed invention is enabled.

3. Whether the claimed invention is indefinite.

4. Whether the amendment of June 10, 2003 should be entered.

7. Grouping of the Appealed Claims:

The claims on appeal may be grouped as follows: 1) claims 12, 15, and 16; 2) claim 13; and 3) claim 14.

8. Arguments:

1. Whether there is a written description of claims 12, 14, and 15.

The claims are rejected for various reasons under 35 USC 112 for lack of a written description. The rejection is traversed. The issues are discussed below.

(1) Specific linkage sites

Specific linkage sites between the moities need not be recited since these can be readily known to one of ordinary skill in the art for the reasons which follow.

Moiety "A"

A is a solid support selected from standard materials applied in solid phase and solution phase organic chemistry. In the present application on page 1, under "Technical Field" it is stated:

> "The present invention relates to the field of ultra high-throughput screening on the solid support and in homogeneous solution by a novel generic labeling technology. The new labeling technology is based on new chemically stable fluorophores, which possess reactive chemical functionalities for attachment to a solid support and subsequent start of combinatorial synthesis of compound libraries."

From this it is immediately evident that "A" must be such that it is be useful in screening techniques and in combinatorial synthesis of compound libraries. Such solid support and specific linking sites for linking chemical compounds to such solid support are known (see, e.g. Fruechtel, J. S.; Jung, G. Organic chemistry on solid supports. Angew. Chem., Int. Ed. Engl. (1996), 35(1), 17-42). See also In the present application:

- Example 3B a "Rink amide resin", see e.g. Rink H., Solid-phase synthesis of protected peptide fragments using a trialkoxy-diphenyl-methyl ester resin; Tetrahedron Lett. (1987), 28(33), 3787-90, and
- Example 5B an aminoethyl-Tentagel resin, see e.g. Fruechtel, J. S.; Jung, G. Organic chemistry on solid supports. Angew. Chem., Int. Ed. Engl. (1996), 35(1), 17-42.

Therefore, it is deemed that a skilled man is immediately aware of the nature of "A" and the chemical binding to "B".

Moiety "B"

A linker is by definition a chemical moiety which connects two or more chemical entities. According to the present invention said linker must allow cleavage of the fluorescent conjugates for liberation of the D and C containing fragments. Such linkers are known and include benzyl, benzhydryl, benzhydryliden, trityl, xanthenyl, benzoin, silicon, or allyl based linkers (claim 13). Exemplified linkers are a benzhydryl group and a benzyl group in examples 3B, 5B, 6B, and 7B. It is immediately evident that the specific linkage sites between the moiety A and B must be such that the linker can be chemically reacted with a chemically reactive group which is part of a solid support. The specific linkage site is clearly dependent on the chemical nature of "A" and of "B". According to Example 3B this is a hydroxy group, according to examples 5B and 7B it is an amide group. The same is true for the specific linkage site between B and D, or B and C (e.g., which is according to example 3B conveniently an amide bond), or B and E (e.g., which is according to example 5B and 7B conveniently an amide bond).

Moiety "C"

Possible specific linkage sites are clearly defined in a compound of formula I and include those where a residue R_1 to R_6 is attached to a phenyl group in a compound of formula I. (The compounds of formula I were allowed in the parent application, now USP 6,207,831.)

Moiety "D"

A spacer is by definition a chemical moiety which connects two or more chemical entities and which provides space between two chemical entities which are attached via a spacer. A spacer D or D´ includes according to the present invention α,ω-diamino-alkanes, diaminocyclohexyl, bis-(aminomethyl)-substituted phenyl, α-amino-ω-hydroxy-alkanes, alkylamines, cyclic alkylamines, cyclic alkyldiamines, or amino acids without or with additional functionality in the side chain. Such a spacer has, e.g., two reactive groups which are suitable for connecting two chemical entities, e.g., two amine groups, amino and hydroxy groups, carboxy and amine groups, etc. The specific linkage site is thus, depending on the chemical nature of the spacer used, clearly defined for a man of ordinary skill.

From the present application there is sufficient guidance and a skilled man is immediately aware of what chemical nature the specific linkage sites of A, B, C, D and D' can be. A more precise definition would improperly narrow the scope of protection to which the applicants are entitled, given the nature of the invention.

(2) Functional terms

The inventors are entitled to functional language in the claims because from the functional language a man of ordinary skill is immediately able to carry out the invention without undue experimentaion.

re: Solid Support Nothing is deemed to be vague or open-end about this list of supports, which are all standard materials which are used in solid phase and liquid phase organic syntheses. There is a broad range of solid supports and they exhibit a broad range of properties. For example, a support may be a solid in one phase (e.g., an ether) and be soluble in another phase, (e.g., an alcohol or water). (See, e.g., the references cited above; Bayer E., Mutter M. Liquid phase synthesis of peptides, Nature, 237:512-513, 1972; and Hermkens et al., Solid-Phase Organic Reactions II. Tetrahedron 53(16), 5643-5678, 1997.) The nature of these supports, how to form linkages to these supports, etc. are not vague or indefinite but rather are all matters of common knowledge to synthetic chemists.

re: B-portion of the claimed molecule

The arguments made above are incorporated herein.

The Examiner has represented the present claims and field of technology in two ways, both of which are incorrect. First, the Examiner states that "the claims could encompass an infinite number of variations". This is a factually incorrect statement. Although the generic claim covers a large number of compounds, the compounds are not infinite in number. If an infinite claim had been presented for examination, there might be some basis for rejection, since no amount of exemplification would approach infinity. This mis-characterization of the claims is inappropriate and should be withdrawn or supported. The rejections based on this mis-characterization must also be withdrawn. A rejection must be based on what is being claimed, not on the Examiner's mis-statement thereof. The Examiner has also mis-stated the level of predictability in this art. The Examiner repeatedly has referred to the "unpredictability of the art". Although unpredictability can be fundamental basis for rejections, the Examiner neither defines what this unpredictability level is nor provides any support whatsoever for stating that this art is unpredictable. To the contrary, it is deemed that the field of combinatorial synthesis on solid supports is a mature art with a high level of predictability with regard to synthetic methods. In support of this statement, the claims from various patents in this field have been made of record.

USP 6,721,099 claims a solid support with a compound attached thereto. The Examiner's attention is directed to the following terms, which are not further defined in claim 1: solid support, identifier, CEC' is a tag, $F^{1'}$ is a functional group, and F^2 is a linking component. None of these terms provide structural limitations or points of attachment and they use "functional" language: e.g., identifier, tag, functional, and linking. The claims are very broad.

Similarly, USP 6,503,759 claims a solid support with a compound attached thereto. The Examiner's attention is directed to the following expression in claim 1: "said identifiers being bound to said solid support either directly or indirectly or through other than a tag component of another identifier."

Similarly, USP 5,766,963 claims a chemical library. The Examiner's attention is directed to the following terms, which are not further defined in claim 1: S is a solid support, L is a first linker, L' is a second linker, and T" is a tag.

The Examiner dismisses these patents on the basis that the allowance of claims in other cases is immaterial. Applicants disagree. Whereas such allowances are not controlling, they are not immaterial. These patents, as well as many of the numerous technical publications and patents cited on their first pages, are evidence that chemical synthesis on solid supports is a mature art wherein terms such as "linker", "solid support", "functionalized", etc. are commonly used without need of further definition or limitation in order to be understood by one of ordinary skill in the art. The grant of these three US patents (which were examined by three different examiners) demonstrates that these expressions meet the requirements of 35 USC 112. These patents also demonstrate that compound claims need not recite specific points of attachment between different moieties to meet the requirements of 35 USC 112. (If necessary, additional

examples of US patents could be provided.) The point of these citations (both to US patents and to technical publications) is that they reflect the state of the art and the language of this technology. The terms rejected by the Examiner are the terms used by practitioners in the art. Not only is this evidenced by the technical publications but it has been recognized by the USPTO. The Examiner cannot apply an arbitrary standard which is stricter that that recognized by the relevant art nor can the Examiner dismiss these patents are immaterial.

The Examiner has recited U. of Ca. vs Lilly (43 USPQ2d, 1398) in support of the rejection. However, this case is fully supportive of applicants' arguments. In Lilly, the court clearly distinguishes between DNA cases and chemical cases. At page 1406, the court states that in chemical cases a generic formula "is normally an adequate description" whereas with genetic material it is not. The Examiner has also mis-stated the law with regard to examples. The Examiner states that "adequate disclosure ... requires *representative examples*" (Examiner's emphasis). The court in Lilly disagrees ": "Mention of representative compounds ... clearly is not required by § 112 or by any other portion of the statute". The Examiner's response is that the present claims are not generic because they are open-ended. This response is inapposite since applicants' comment on Lilly is that the court distinguished between the adequacy of description for chemical vs DNA cases. Clearly the present cases are chemical in nature.

2. Whether claims 12, 15, and 16 are enabled.

The claims are also rejected for various reasons under 35 USC 112 for lack of enablement. The rejection is traversed. The issues are substantially identical to those raised by the Examiner under the rejection for lack of written description and the responses thereto are similar to those above, which are incorporated herein. Comments regarding sufficiency of examples and predictability in the art follow.

The claims are all limited in the "C" portion to the compounds of formula I granted in parent US patent 6,207,831. "C" makes the claimed compounds fluorescent. Thus, each compound claimed inevitably has the property of having the advantageous fluorescent characteristics of "C". Thus, a man of ordinary skill has not only a reasonable expectation of success but will inevitably succeed in obtaining compounds having fluorescent characteristics when using his skill to prepare compounds as claimed in the present invention. Thus, the present scope is not an invitation to undue experimentation, as argued by the Examiner.

Furthermore, there are disclosed a total of 17 compounds (in Example 3B two compounds, in Example 5B ten compounds , in Example 6B four compounds, and in Example 7B one compound). Additionally, there are several representative examples for specific linkages between the different portions of the molecules claimed. Given knowledge in the art and the

teachings in the specification, it is deemed that this is a sufficient number of examples to support the claim scope.

The Examiner states that once an Examiner has established a *prima facie* case of lack of enablement, the burden shifts to the applicant. For the reasons provided above, it is deemed that a *prima facie* case has not been established.

3. Whether claims 12, 15, and 16 are indefinite.

The claims are also rejected for various reasons under 35 USC 112 for indefinitness. The rejection is traversed. It is again noted that many of the issues are substantially identical to those raised by the Examiner under the rejection for lack of written description and the responses thereto are similar to those above, which are incorporated herein. Some of the issues are further discussed below.

"Based" and "functionalized surfaces" These are not relative terms. They are only used herein in association with solid supports, which, as discussed above, are well know to the man of ordinary skill in the art of synthetic chemistry, especially since these are standard materials. Surfaces bearing reactive functional groups are commercially available.

"Open-ended" recitations The dashes on D and D' in the formulas are points of attachment. This is not confusing to one in the chemical arts.

4. Whether claim 13 is described, enabled, and definite.

The claim is rejected for the same reasons as discussed above. The rejection is traversed for the reasons provided above. Furthermore, this claim further limits moiety B to specific chemical entities. Therefore, any rejections based on B are deemed to be moot.

5. Whether claim 14 is described, enabled, and definite.

The rejections described above have also been made against claim 14. The rejection is traversed. The claim is directed to compounds defined in terms of specific structures. There is no element of the claims which is not specifically shown except for "A". The arguments presented above are repeated herein. Regarding the rejection because claim 14 is not properly dependent on claim 12, a dependent claim can further limit an element recited in a prior claim. However, a dependent claim can also add an element which has not been recited in a prior claim, as long as said claim is not limited by language such as "consisting of".

6. Whether the amendment of June 10, 2003 should be entered.

The claims have also been rejected under 35 USC 112 because of the term "Tentagel" and because of improper Markush language. The amendment of June 10, 2003 mooted both these issues but was not entered even though the Examiner states (Advisory Action) that entry would obviate *some* (not defined by the Examiner) grounds of rejection. The Examiner further states that the amendment would not place the case in better form for appeal. Applicants traverse. If the claims were entered and some issues would be obviated, then the case would be in better condition for appeal. It is requested that the new claims be entered, that the Tentagel and Markush issues be withdrawn, and that the appeal proceed on the basis of claims 17-21.

It is believed that none of the claims are defective under 35 USC 112. Accordingly, reconsideration of the propriety of the outstanding rejections under 35 U.S.C. 112 allowance of the claims to issue as U.S. Letters Patent is respectfully solicited.

The Commissioner is hereby authorized to charge the fee under 37 CFR 1.17(c) of $320.00 to Deposit Account No. 19-0134

Respectfully submitted,

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Encls.: Appeal Brief in triplicate with Appendices I and II
This page in duplicate
Date: September 30, 2003

APPENDIX I

CLAIMS ON APPEAL

12. Compounds comprising structures of the formulae II–III

A-B-D-C-D´- (Formula (II))

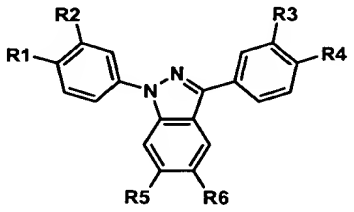
A-B-D- and -D´-C (Formula (III))

wherein

A is selected from the group consisting of functionalized polystyrene based resins, polyacrylamide based polymers, polystyrene/polydimethylacrylamide composites, PEGA resins, polystyrene-polyoxyethylene based supports, Tentagel resins, PEG-polystyrene graft polymeric supports, glass surfaces, functionalized surfaces, materials grafted with functionalized surfaces, and polyethylenglycol;

B is a linker allowing cleavage of fluorescent conjugates of formula (II-III) for liberation of the D and C containing fragments;

C is a compound selected from formula (I)



(I)

wherein

one of the radicals R^1 or R^2 and one of the radicals R^3 or R^4 is hydrogen and the other is independently –COOH, $-COOR^7$, $-CONH_2$, $-CONH(CH_2)_nOH$, $-CONR^8R^9$, $-CH_2OH$, $-CH_2NH_2$, $-NO_2$, $-NR^{10}R^{11}$, $-NHCOR^{12}$, Cl, Br, F, $-CF_3$, -N=C=O, -N=C=S, $-SO_3H$, $-SO_2NH(CH_2)_nNH_2$, (C_1-C_4) alkyl, (C_1-C_{16})-alkyl substituted at the terminal carbon with –COOH, $-COOR^7$, $-CONH_2$, $-CONR^8R^9$, $-CONH(CH_2)_nOH$, $-CH_2OH$, $-CH_2NH_2$, -N=C=O, -N=C=S, $-SO_3H$, $-SO_2NH(CH_2)_nNH_2$, $-CONH(CH_2)_nNH_2$, and the $-NH_2$ group could also be substituted by (C_1-C_4) alkyl or a commonly used amino protecting group;

and one of the radicals R^5 or R^6 is hydrogen and the other is hydrogen, halogen, $-NO_2$, $-NR^{10}R^{11}$, $-NHCOR^{12}$, (C_1-C_4) alkyl, (C_1-C_{16})-alkyl substituted at the terminal carbon with –COOH, $-COOR^7$, $-CONH_2$, $-CONR^8R^9$, $-CONH(CH_2)_nOH$, $-CH_2OH$, $-CH_2NH_2$, -N=C=O, -N=C=S, $-SO_3H$, $-SO_2NH(CH_2)_nNH_2$, $-CONH(CH_2)_nNH_2$, wherein and the $-NH_2$ group could also be substituted by $(C_1- C_4)$ alkyl or a commonly used amino protecting group;

n is 2–8;

with the *proviso* that only one of R^1-R^6 is nitro;

R^7 is a commonly used carboxyl protecting or carboxyl activating group;

R^8 or R^9 is hydrogen and the other is lower alkyl (C_1-C_4), phenyl, benzyl, or R^8 and R^9 are part of a 5 or 6 membered ring;

R^{10} and R^{11} are independently hydrogen or (C_1-C_4)alkyl; and

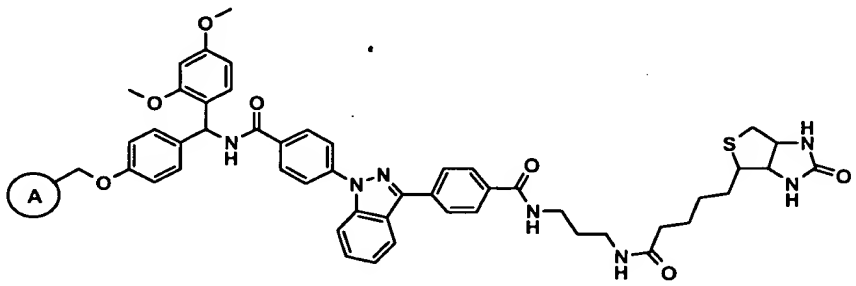
R^{12} is (C_1-C_{10})alkyl, phenyl, which both can be substituted by (C_1-C_4) alkyl, protected amino group or halogen; and

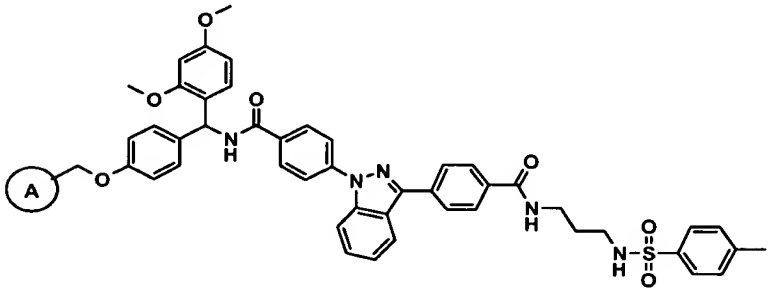
D and D´ are independently a bond or a spacer selected from α,ω-diamino-alkanes, diaminocyclohexyl, bis-(aminomethyl)-substituted phenyl, α-amino-ω-hydroxy-alkanes, alkylamines, cyclic alkylamines or cyclic alkyldiamines or amino acids without or with additional functionality in the side chain.

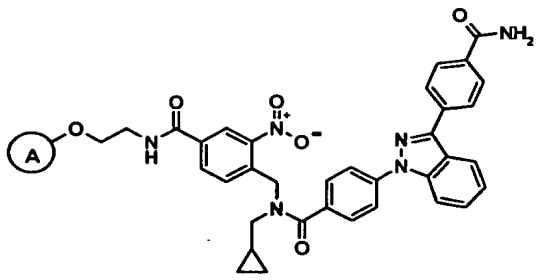
13. Compounds of claim 12, wherein

B is selected from benzyl, benzhydryl, benzhydryliden, trityl, xanthenyl, benzoin, silicon, or allyl based linkers.

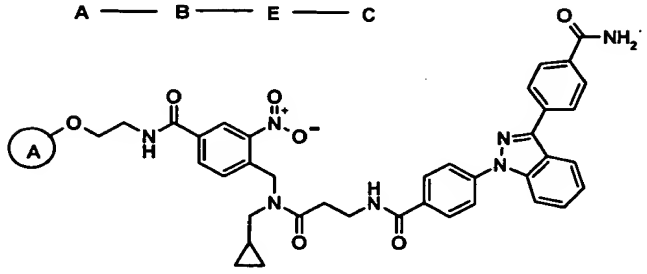
14. Compounds of claim 12 of the following structures:







A — B — E — C

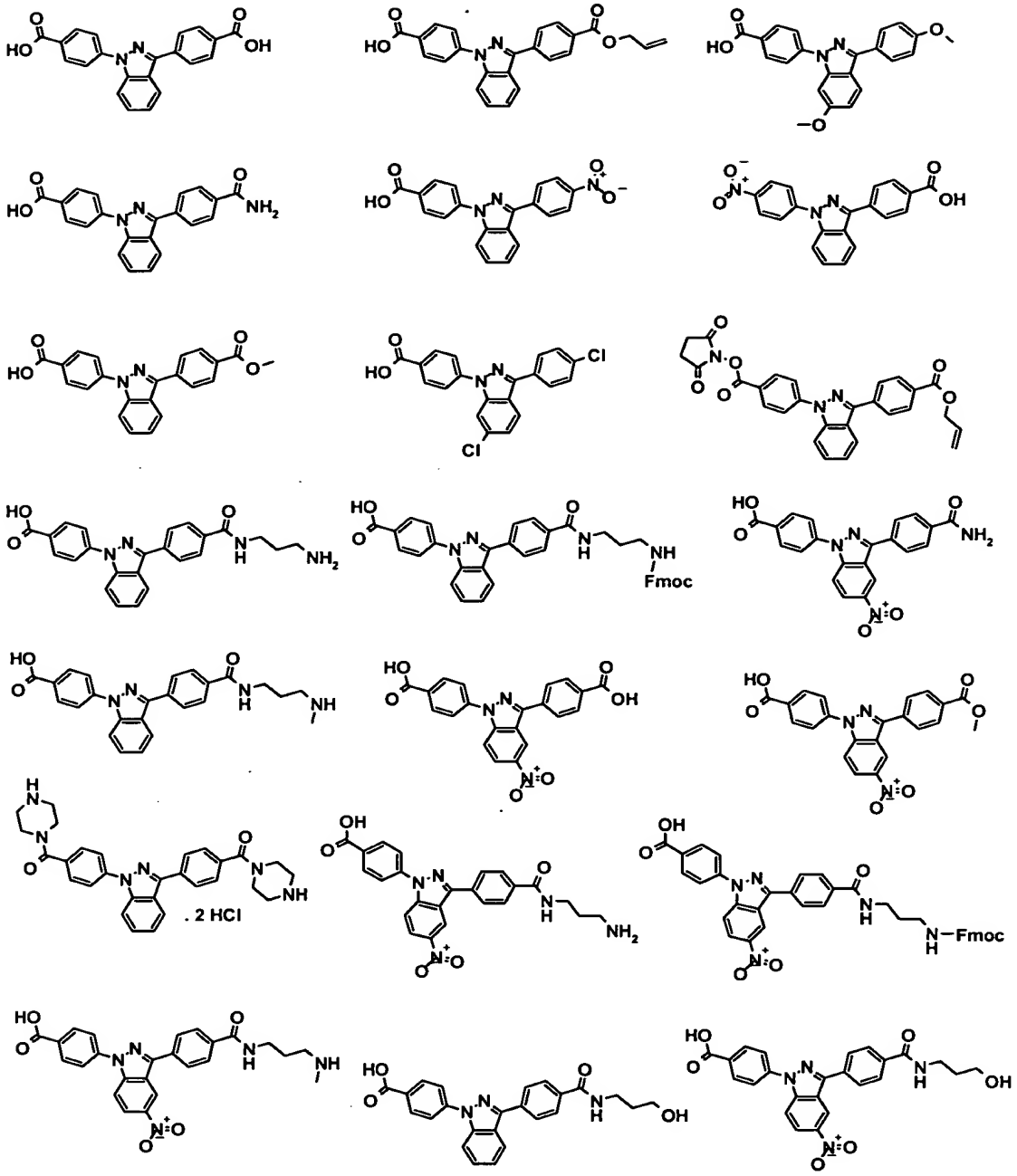


A — B — E — D' — C

A — B — D — E — C

15. Compounds of claim 12 wherein the amino protecting group is *tert*-butyloxycarbonyl, 9-fluorenylmethoxycarbonyl, phthalimido, trifluoroacetamido, methoxycarbonyl, ethoxycarbonyl, benzyloxycarbonyl, allyloxycarbonyl, 2,2,2-trichloroethoxycarbonyl, or 2-(trimethylsilyl)ethoxy-carbonyl.

16. Compounds of claim 12 wherein C is of the following structures:


. 2 HCl
Fmoc

APPENDIX II

NON-ENTERED CLAIMS

17. Compounds comprising structures of formula II or of formula III

A-B-D-C-D´- (Formula II)

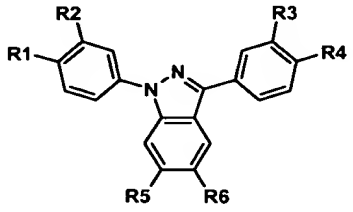
A-B-D- and -D´-C (Formula III)

wherein

A is selected from the group consisting of functionalized polystyrene based resins, polyacrylamide based polymers, polystyrene/polydimethylacrylamide composites, PEGA resins, polystyrene-polyoxyethylene based supports, polystyrene/divinylbenzene-PEG graft copolymers, PEG-polystyrene graft polymeric supports, glass surfaces, functionalized surfaces, materials grafted with functionalized surfaces, and polyethylenglycol;

B is a linker allowing cleavage of fluorescent conjugates of formula II or of formula-III for liberation of the D and C containing fragments;

C is a compound selected from formula (I)



(I)

wherein

one of the radicals R^1 or R^2 and one of the radicals R^3 or R^4 is hydrogen and the other is independently –COOH, $-COOR^7$, $-CONH_2$, $-CONH(CH_2)_nOH$, $-CONR^8R^9$, $-CH_2OH$, $-CH_2NH_2$, $-NO_2$, $-NR^{10}R^{11}$, $-NHCOR^{12}$, Cl, Br, F, $-CF_3$, -N=C=O, -N=C=S, $-SO_3H$, $-SO_2NH(CH_2)_nNH_2$, (C_1-C_4) alkyl, (C_1-C_{16})-alkyl substituted at the terminal carbon with –COOH, $-COOR^7$, $-CONH_2$, $-CONR^8R^9$, $-CONH(CH_2)_nOH$, $-CH_2OH$, $-CH_2NH_2$, -N=C=O, -N=C=S, $-SO_3H$, $-SO_2NH(CH_2)_nNH_2$, $-CONH(CH_2)_nNH_2$, and the $-NH_2$ group could also be substituted by (C_1-C_4) alkyl or a commonly used amino protecting group;

and one of the radicals R^5 or R^6 is hydrogen and the other is hydrogen, halogen, $-NO_2$, $-NR^{10}R^{11}$, $-NHCOR^{12}$, (C_1-C_4) alkyl, (C_1-C_{16})-alkyl substituted at the terminal carbon with –COOH, $-COOR^7$, $-CONH_2$, $-CONR^8R^9$, $-CONH(CH_2)_nOH$, $-CH_2OH$, $-CH_2NH_2$, -N=C=O, -N=C=S, $-SO_3H$, $-SO_2NH(CH_2)_nNH_2$, $-CONH(CH_2)_nNH_2$, wherein and the $-NH_2$ group could also be substituted by (C_1-C_4) alkyl or a commonly used amino protecting group;

n is 2–8;

with the *proviso* that only one of R^1-R^6 is nitro;

R^7 is a commonly used carboxyl protecting or carboxyl activating group;

R^8 or R^9 is hydrogen and the other is lower alkyl (C_1-C_4), phenyl, benzyl, or R^8 and R^9 are part of a 5 or 6 membered ring;

R^{10} and R^{11} are independently hydrogen or (C_1-C_4)alkyl; and

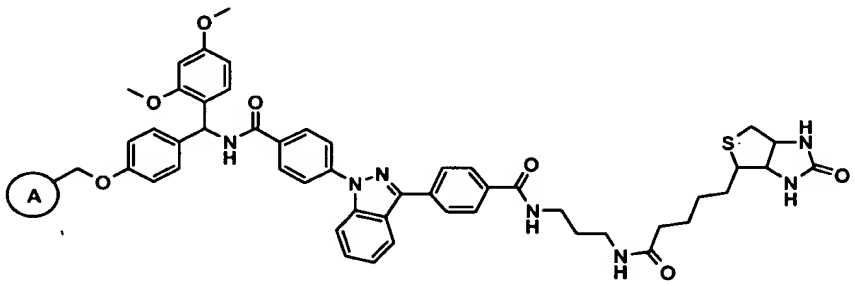
R^{12} is (C_1-C_{10})alkyl, phenyl, which both can be substituted by (C_1-C_4) alkyl, protected amino group or halogen; and

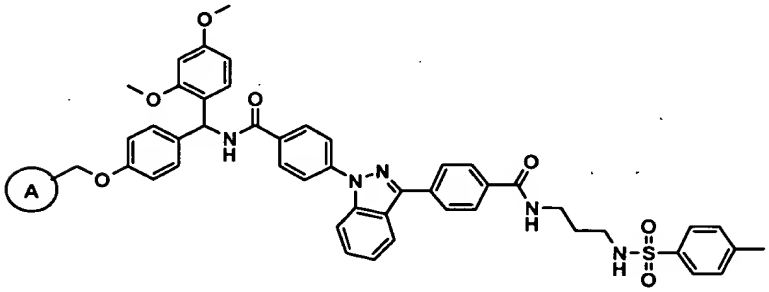
D and D´ are independently a bond or a spacer selected from α,ω-diamino-alkanes, diaminocyclohexyl, bis-(aminomethyl)-substituted phenyl, α-amino-ω-hydroxy-alkanes, alkylamines, cyclic alkylamines or cyclic alkyldiamines or amino acids without or with additional functionality in the side chain.

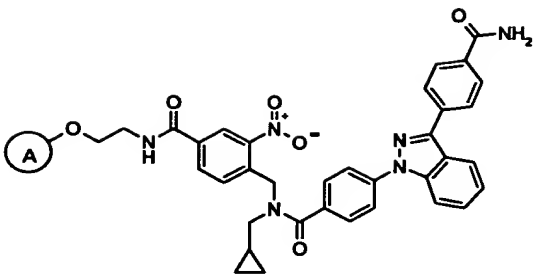
18. Compounds of claim 17, wherein

B is selected from benzyl, benzhydryl, benzhydryliden, trityl, xanthenyl, benzoin, silicon, or allyl based linkers.

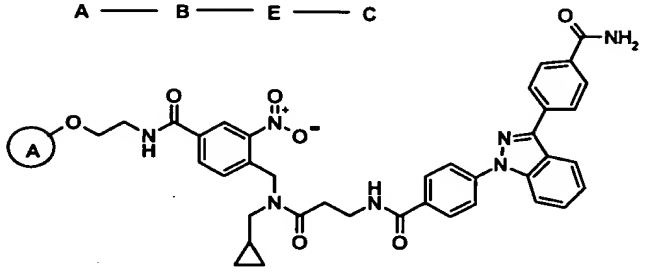
19. Compounds of claim 17 of the following structures:







A — B — E — C

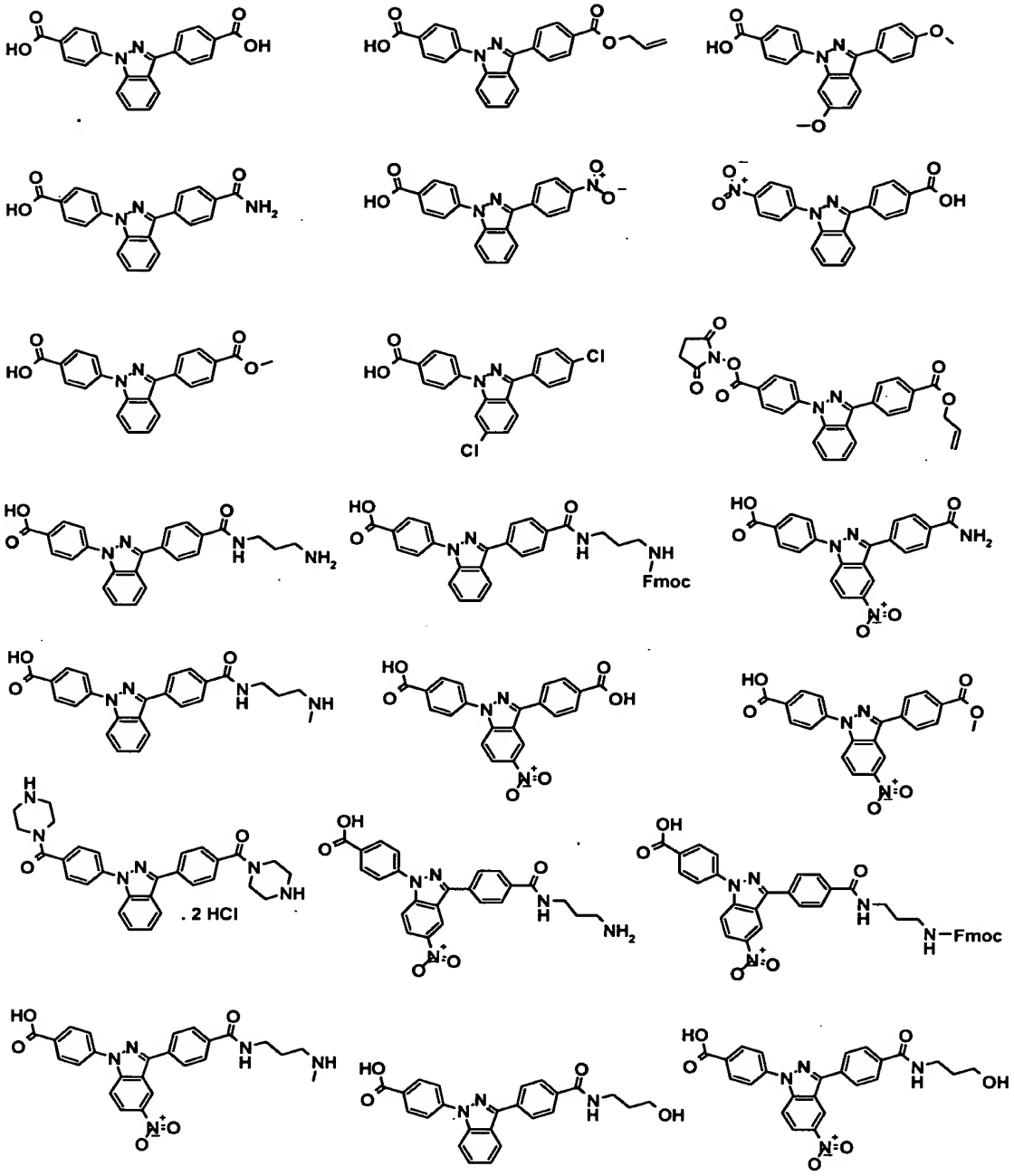


A — B — E — D′ — C

A — B — D — E — C

20. Compounds of claim 17 wherein the amino protecting group is *tert*-butyloxycarbonyl, 9-fluorenylmethoxycarbonyl, phthalimido, trifluoroacetamido, methoxycarbonyl, ethoxycarbonyl, benzyloxycarbonyl, allyloxycarbonyl, 2,2,2-trichloroethoxycarbonyl, or 2-(trimethylsilyl)ethoxy-carbonyl.

21. Compounds of claim 17 wherein C is of the following structures:


. 2 HCl
Fmoc